

The University of Chicago

THE ACTION OF INSULIN ON THE MOTILITY OF THE EMPTY STOMACH

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE BIOLOGICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

1933

By
JAMES FRANCIS REGAN

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THE ACTION OF INSULIN ON THE MOTILITY OF THE EMPTY STOMACH

J. F. REGAN

From the Physiological Laboratory of the University of Chicago

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In 1924 Bulatao and Carlson reported that the subcutaneous injection of insulin into normal fasting dogs increased the motility of the stomach. The increase in gastric tonus and in height and frequency of the contractions usually appeared in 50 minutes, developing into gastric tetany in one hour after injection. On injecting 20 to 40 units of insulin subcutaneously into the diabetic dog there was at first no influence on the gastric tonus and hunger contractions. Fifteen to twenty minutes after the insulin injection the gastric tonus began to decrease, and the hunger contractions became gradually weaker with longer intervals of rest, until at 30 to 60 minutes following the insulin, the stomach became relatively atonic and quiescent. This quiescence may last from 10 to 20 minutes, when the hunger contractions and gastric tonus return gradually and the typical gastric tetany of hypoglycemia appears 60 to 80 minutes after insulin administration. They stated that the primary action of insulin on the gastric tonus and hunger contractions is inhibition and that the gastric tetany of hypoglycemia comes later.

Quigley, Johnson and Solomon reported that the subcutaneous injection of insulin usually produced in normal fasting humans an increase in gastric motility. Templeton and Quigley reported that intravenous or subcutaneous injection of insulin inhibited the motility and depressed the tone of a Heidenhain pouch. Quigley and Templeton reported that insulin inhibited gastric hunger contractions in dogs having the vagi sectioned. Simici, Guiera and Dimitriu reported that the injection of insulin in normal fasting men inhibited gastric motility. Mulinos reported similar results on dogs.

METHOD. Five dogs, weighing from 13 to 17 kgm., with gastric fistulae, were used. These dogs were trained to lie quietly during the experiments which were from 3 to 9 hours' duration. All experiments were performed after at least 18 hours' starvation. The dogs were kept on a constant diet and were in good condition.

The gastric movements were recorded by means of a rubber balloon attached to a water manometer. The balloon was inflated with a

constant amount of air. A flexible wire connected to a spring was placed within the balloon in order to keep it from moving around in the stomach. This device enabled one to get constant records from day to day. The balloon was placed in the pyloric end of the stomach and anchored there. The insulin used in these experiments was the "Iletin" of Eli Lilly & Company.

Records were run on the dogs until the normal was established before beginning to inject insulin. Before each injection a control record was run for from 2 to 6 hours. The insulin was injected either intravenously or subcutaneously in doses of 2 to 30 units. The record was continued without interruption until the animal became very restless or went into convulsions (usually about $1\frac{1}{2}$ to 2 hours after insulin) in which event glucose was administered intravenously or into the stomach. The glucose was given in the form of a 30 per cent solution and was given in amounts of 4 to 40 grams.

Injections were made during the height of gastric motor activity and in quiescent periods. Ringer's solution or physiological saline was injected

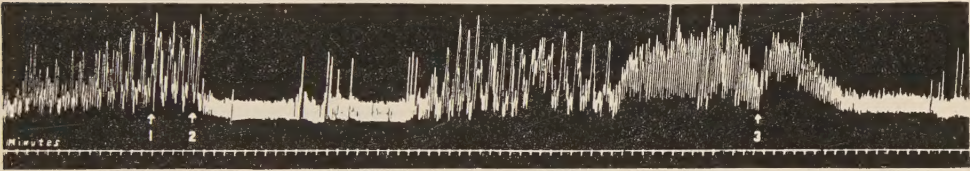


Fig. 1. Dog fasting 18 hours in normal gastric hunger period. 1, injection of 1 cc. Ringer's solution intravenously. 2, injection of 20 units insulin intravenously. 3, introduction of 30 grams glucose into the stomach through the gastric fistula.

preceding the insulin in order to rule out the effect of the injection itself. Blood samples were taken and blood sugar determinations made. These results will be published as soon as sufficient data are accumulated.

RESULTS. When 10 to 20 units of insulin were injected subcutaneously into normal dogs during a hunger period, there was at first no influence on the gastric tonus and hunger contractions; a few minutes after the insulin injection the gastric tonus began to decrease, and the hunger contractions became gradually weaker with longer intervals of rest until, on the average 18 minutes following the insulin, the stomach became relatively atonic and quiescent. This quiescence may last for from 15 to 60 minutes, when hunger contractions and gastric tonus return gradually.

On intravenous injection of from 2 to 30 units of insulin into normal dogs during a hunger period there was a fall in tone and quiescence within one minute after injection. Generally the stomach contracted once after the injection and then became quiet. This quiescent period lasted from

3 to 45 minutes depending upon the dosage, when contractions and gastric tonus return. This activity resembles very closely type III gastric activity as classified by Carlson. The dogs then became very restless, salivated, whined and sometimes went into convulsions. The intravenous injections of glucose relieved these symptoms and caused a gradual fall in tone and a diminution of activity followed by quiescence.

In order to determine whether or not this inhibition was due to impurities in the insulin preparations, we obtained some crystalline insulin from the Connaught Laboratories. The crystals were dissolved in hydrochloric acid at a pH of from 2 to 3. We injected 0.01 N hydrochloric acid as a control. There was no effect shown on the tracing. The injection of from 2 to 20 units of the crystalline insulin intravenously produced the same type of response as the commercial preparation.

Mulinos has reported that the failure of insulin to produce gastric hyperactivity was due to the lack of some dietary factor, probably vitamin B. It was thought that this might be the cause of the inhibition following intravenous injection of insulin. Two dogs, therefore, were fed 25 grams of fresh yeast daily along with their regular diet of bread, cooked meat and milk for one month. No detectable changes were recorded on the tracings.

In order to rule out the action of the insulin preservative 0.2 per cent phenol in 0.01 N hydrochloric acid was injected intravenously. No effects on gastric motility were observed.

DISCUSSION. Although this inhibition was not reported by Carlson or Templeton and Quigley on subcutaneous injection, this is probably due to the fact that they considered the cessation of activity as the end of a normal active period. It is probable that the continued but diminishing activity after subcutaneous injection of insulin is a latent period, i.e., the time necessary for the insulin to be absorbed in sufficient quantity to inhibit the activity of the stomach. It is possible to keep the animal's stomach in a state of quiescence for a considerable time by giving repeated doses of insulin. The successive doses were given at the beginning of the tone change.

These results also explain what was thought to be a discrepancy in the effect of insulin on gastric motility in normal and in pancreatectomized dogs. Bulatao and Carlson reported that the injection of insulin into normal fasting dogs increased the motility of the stomach and that in diabetic dogs insulin produced a primary depression of gastric tonus and contractions, followed by increased gastric tonus and contractions when the initial stage of hypoglycemia was reached. The latter has been shown to be the normal reaction on injection of insulin.

It appears that the intravenous injection of insulin stimulates the sympathetic nervous system. There is a fall in tone and a quiescence of the

stomach, accelerations of the heart rate, sweating, constriction of the peripheral blood vessels and dilatation of the pupils in man (see also Cannon, McIver and Bliss). Dworkin has reported that in normal cats and those surviving excision of various portions of the autonomic system the injection of insulin produced the following changes in the heart rate: 1, acceleration due to central sympathico-adrenal impulses; 2, slowing, due to central vagus stimulation; 3, slowing, due to a peripheral action. He has also reported that in the intact animal these changes are expressed in a heart rate that is seldom above the basal level. This is in accord with the work of Templeton and Quigley who reported that the intravenous or subcutaneous injection of insulin inhibits the motility and depresses the tone of a Heidenhain pouch. They reported that the action of insulin in double splanchnicotomized dogs while fasting is similar but slightly greater than that displayed by normal animals. The quiescence continues until the blood sugar falls sufficiently low to cause central parasympathetic stimulation, as is shown by the initiation of gastric motility, slowing of the heart rate, salivation, and constriction of the pupils. If, now, according to Dworkin, both divisions of the autonomic nervous system are stimulated during the insulin hypoglycemia, the parasympathetic system predominates in its influence on the various organs until the convulsive sugar level is reached. This is supported by the facts that insulin inhibits gastric hunger contractions in vagotomized dogs while intravenous injection of glucose is practically without effect on the motility of such a stomach and that the injection of atropine will inhibit the activity of the stomach following insulin.

SUMMARY

1. The intravenous injection of insulin in normal dogs produces a primary depression of tonus and contractions of the stomach followed by an increase in tonus and gastric activity which passes into a regular type III activity, or incomplete gastric tetany.
2. This is a true insulin effect because the same type of response is obtained on injection of crystalline insulin preparations.
3. The insulin response in normal dogs is identical to that reported for pancreatectomized dogs.
4. The increased sympathetic activity and increased adrenalin output after insulin (Cannon, McIver and Bliss) have been correlated with the increased gastric activity (Bulatao and Carlson).

The writer is greatly indebted to Dr. D. A. Scott of the Connaught Laboratories, Toronto, for supplying the crystalline insulin used in these experiments and to Dr. A. J. Carlson under whose direction this work was completed.

BIBLIOGRAPHY

- BULATAO AND CARLSON. 1924. This Journal, lxi, 107.
CANNON, McIVER AND BLISS. 1924. This Journal, lxi, 46.
CARLSON. 1916. The control of hunger in health and disease. Chicago.
DWORKIN. 1931. This Journal, xvi, 311.
MULINOS. 1931. Proc. Soc. Exp. Biol. and Med., xxviii, 520.
QUIGLEY AND TEMPLETON. 1930. This Journal, xci, 475, 482.
TEMPLETON AND QUIGLEY. 1930. This Journal, xci, 467.
SIMICI, GUIREA AND DIMITRIU. 1927. Arch. Malad. Appar. Digest et Malad. Nutrition, xvii, 17.

